

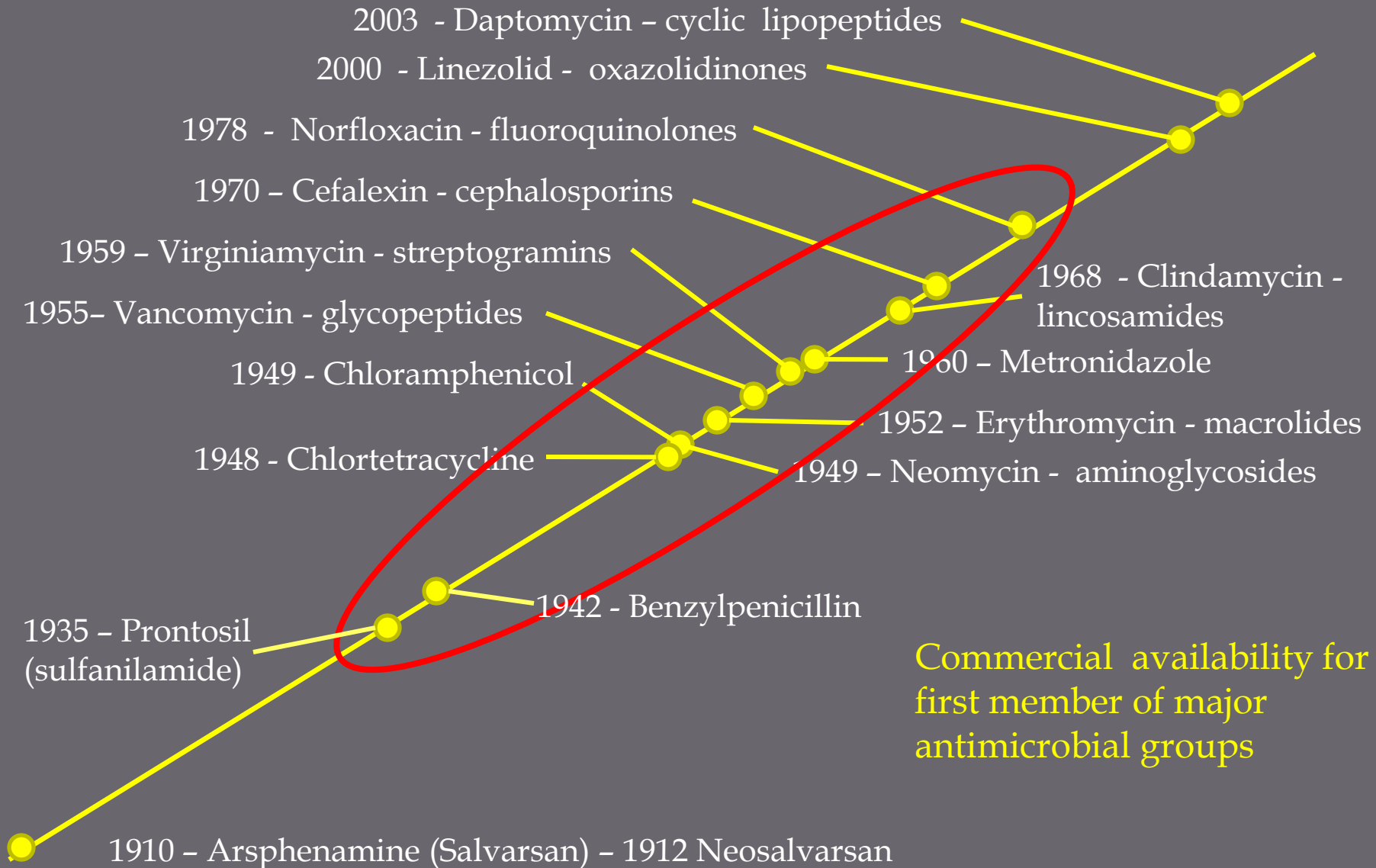
ANIMAL ANTIMICROBIAL USE

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Conflicts

- ▣ Statement in your proceedings
- ▣ What
 - Research (conduct, design, analysis)
 - ▣ Clinical trials (University, contract research, pivotal and non-pivotal)
 - ▣ Pharmacokinetic studies
 - ▣ Bioanalytical analysis
 - Sponsorship (honoraria and expenses) for state, national, and private continuing education
 - Consulting on drug development projects and submissions
- ▣ Who
 - Essentially most animal pharmaceutical companies and multiple producer organizations

Antimicrobial Timeline

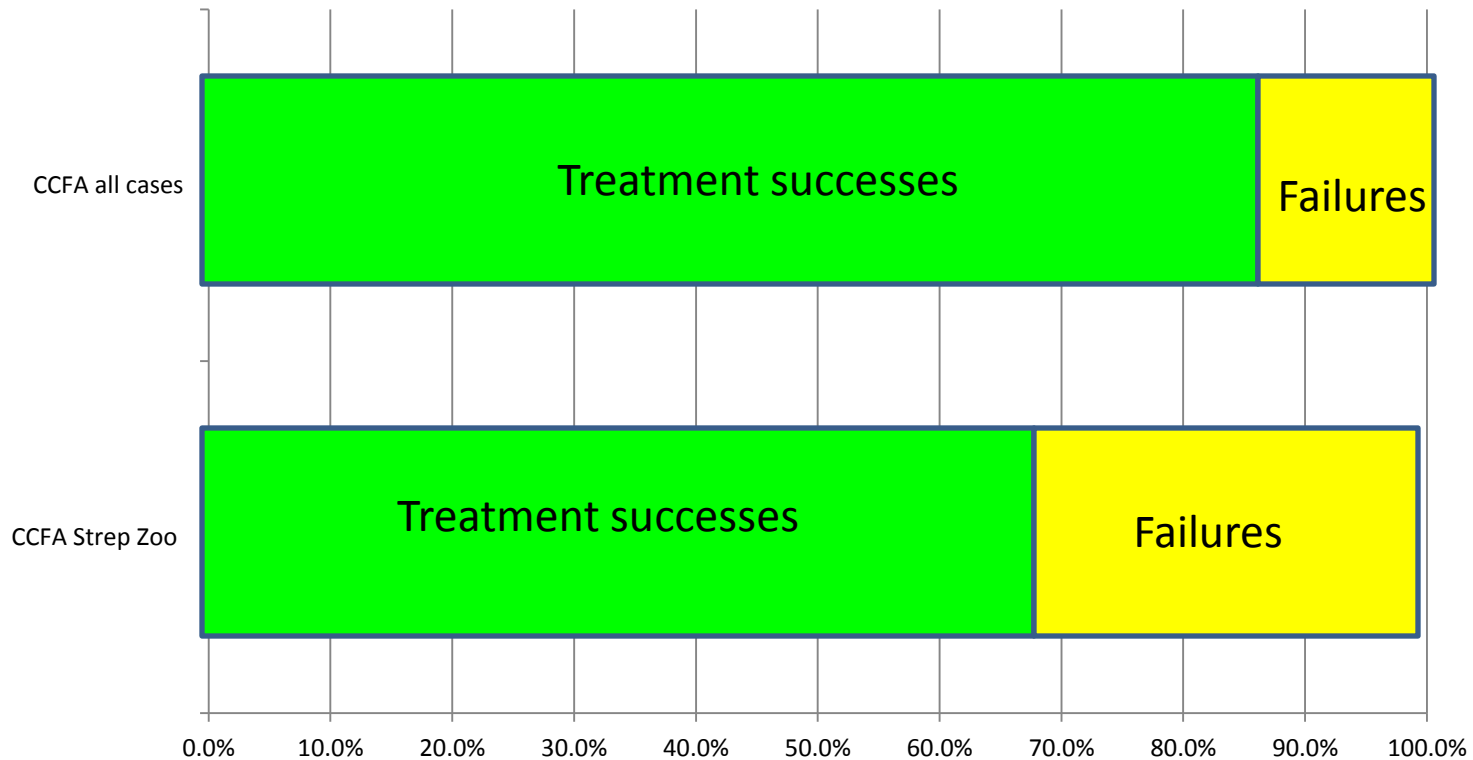


The Basics of Clinical Pharmacology (in one slide)

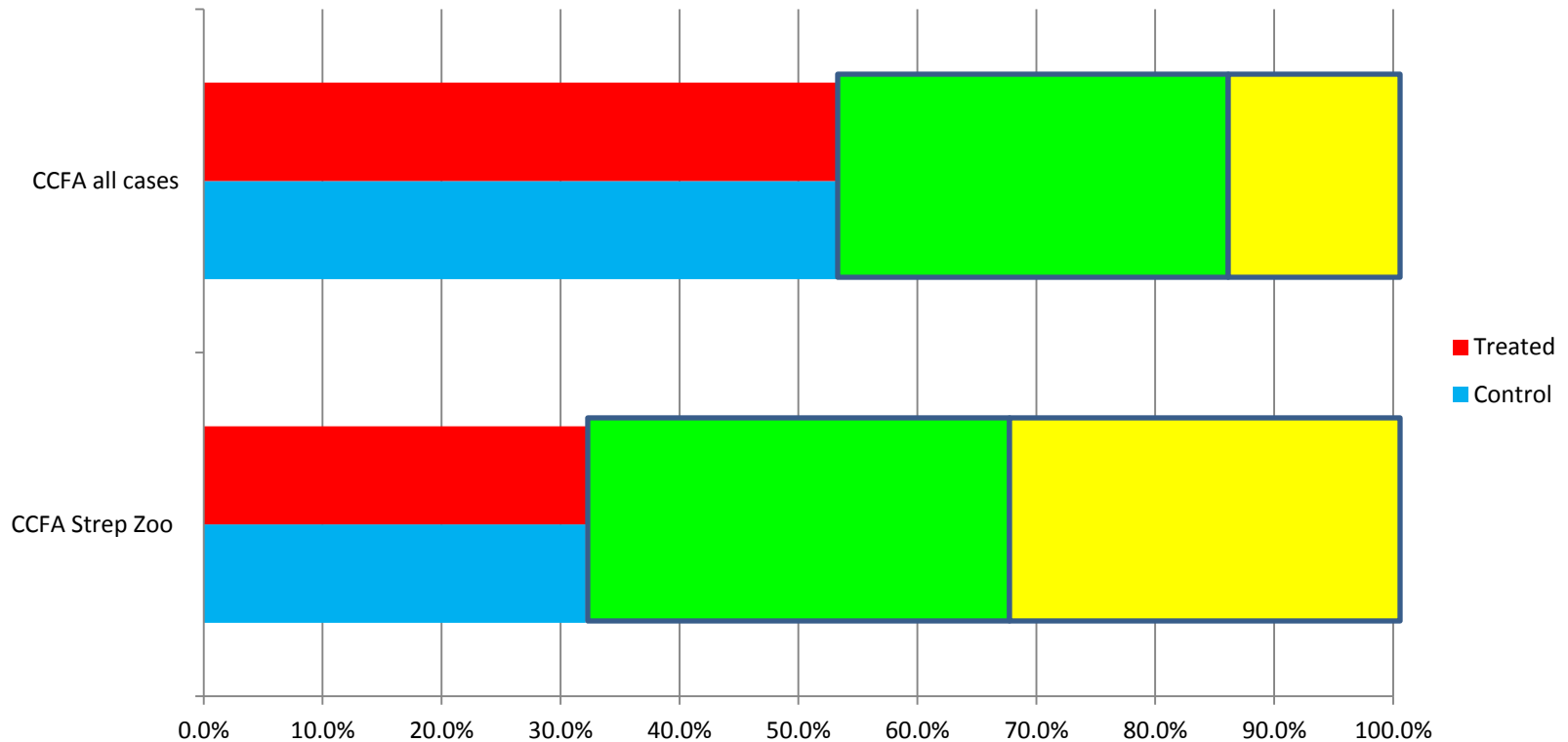
- ▣ Can I do some good?
- ▣ Can I do any harm?
- ▣ Can I get it in the animal(s)?
- ▣ What is the cost?

IF WE ARE GOING TO
CONTEMPLATE THE
BENEFITS AND RISKS OF
ANTIMICROBIALS, MAYBE WE
OUGHT TO CONSIDER WHAT
THEY ACTUALLY DO FOR US

Equine Respiratory Disease



Equine Respiratory Disease



Components of the Resistance Discussion

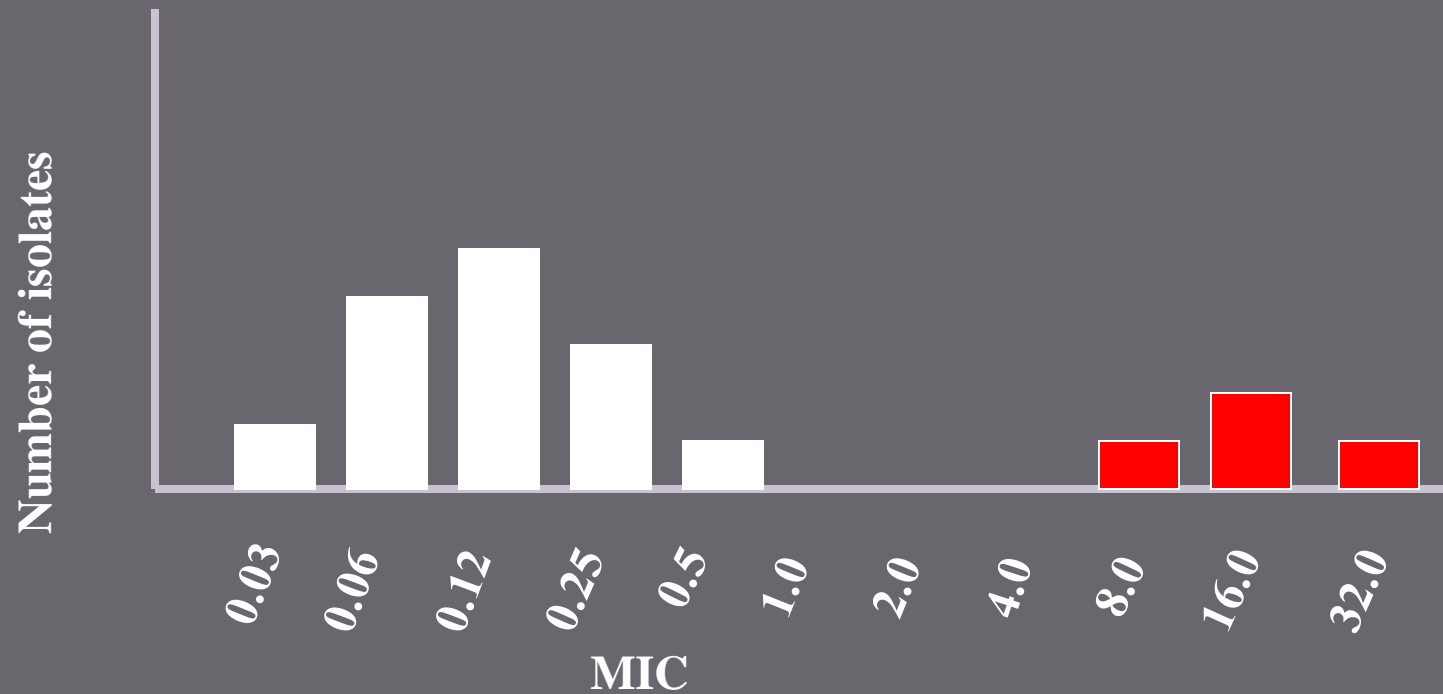
- ▣ We must define and evaluate
 - the definition of resistance
 - the antimicrobial pressure
 - the bacteria of interest
 - the interaction between the antimicrobial and bacteria of interest
 - the outcome of this interaction
 - concern about transfer of resistant bacteria or transmissible resistance elements

**WHO CAN DEFINE
RESISTANCE FOR ME?**

What is resistance?

- ▣ Clinical resistance – **clinical breakpoints**
 - Approved breakpoints are developed from a combination of...
 - ▣ Clinical outcomes coupled with pathogen susceptibility data
 - ▣ MIC distributions of wild type isolate collections
 - ▣ Pharmacokinetic/pharmacodynamic modeling
- ▣ Deviation of susceptibility profiles from the original “wild type” distribution – **epidemiological cutoffs**
 - Determined by MICs determined to be different from the wild type population and/or indicating carriage of a resistance gene

Biphasic Population



**WHAT ANTIMICROBIALS
ARE USED?**

**Table 1. Antimicrobial Drugs Approved for Use in Food-Producing Animals:
2010 Sales and Distribution Data Reported by Drug Class**

Cattle Approvals

	Antimicrobial Class	Annual Totals (kg ¹)	
Domestic	<i>Aminoglycosides</i>	200,794	Oral and FEED neomycin
	<i>Cephalosporins</i> ²	24,588	INJ and IMM ceftiofur, IMM cephapirin
	<i>Ionophores</i>	3,821,138	FEED monensin, lasaslocid
	<i>Lincosamides</i> ²	154,653	IMM pirlimycin
	<i>Macrolides</i> ²	553,229	INJ tilmicosin, tildipirosin, tulathromycin, gamithromycin, tylosin, FEED tylosin and tilmicosin
	<i>Penicillins</i> ²	870,948	INJ and IMM penicillin G, ampicillin
	<i>Sulfas</i> ²	506,218	INJ , WATER, and FEED labels
	<i>Tetracyclines</i> ²	5,592,123	INJ , WATER, and FEED labels
	<i>NIR</i> ^{2,3}	1,517,447	INJ florfenicol, fluoroquinolones, FEED virginiamycin

² Includes antimicrobial drug products which are approved and labeled for use in multiple species, including both food- and nonfood-producing animals, such as dogs and horses.

ORAL (administered individually), IMM (intramammary), INJ (injected individually), FEED (administered through feed to groups), WATER (administered in water to groups)

Approved BRDC Antimicrobials

▣ Single injection

- Tilmicosin (Micotil)
- Florfenicol (Nuflor)
- Ceftiofur Crystalline Free Acid (Excede) **
- Enrofloxacin (Baytril)**
- Danofloxacin (Advocin, formerly A-180)
- Oxytetracycline 200 mg/ml (LA-200, generics) **
- Oxytetracycline 300 mg/ml (Tetradure, generics) **
- Tulathromycin (Draxxin) **
- Gamithromycin (Zactran)
- Tildipirosin (Zuprevo)

****Also labeled for swine respiratory disease**

Approved BRDC Antimicrobials

▣ Multiple injection

- Ceftiofur
 - ▣ Ceftiofur sodium (Naxcel, generics) **
 - ▣ Ceftiofur hydrochloride (Excenel) **
- Oxytetracycline 100 mg/ml (generics)
- Ampicillin trihydrate (Polyflex)
- Tylosin (Tylan, generics) **
- Danofloxacin (Advocin, formerly A-180)
- Procaine penicillin G
- Procaine/benzathine penicillin G
- Sulfadimethoxine (Albon, generics)

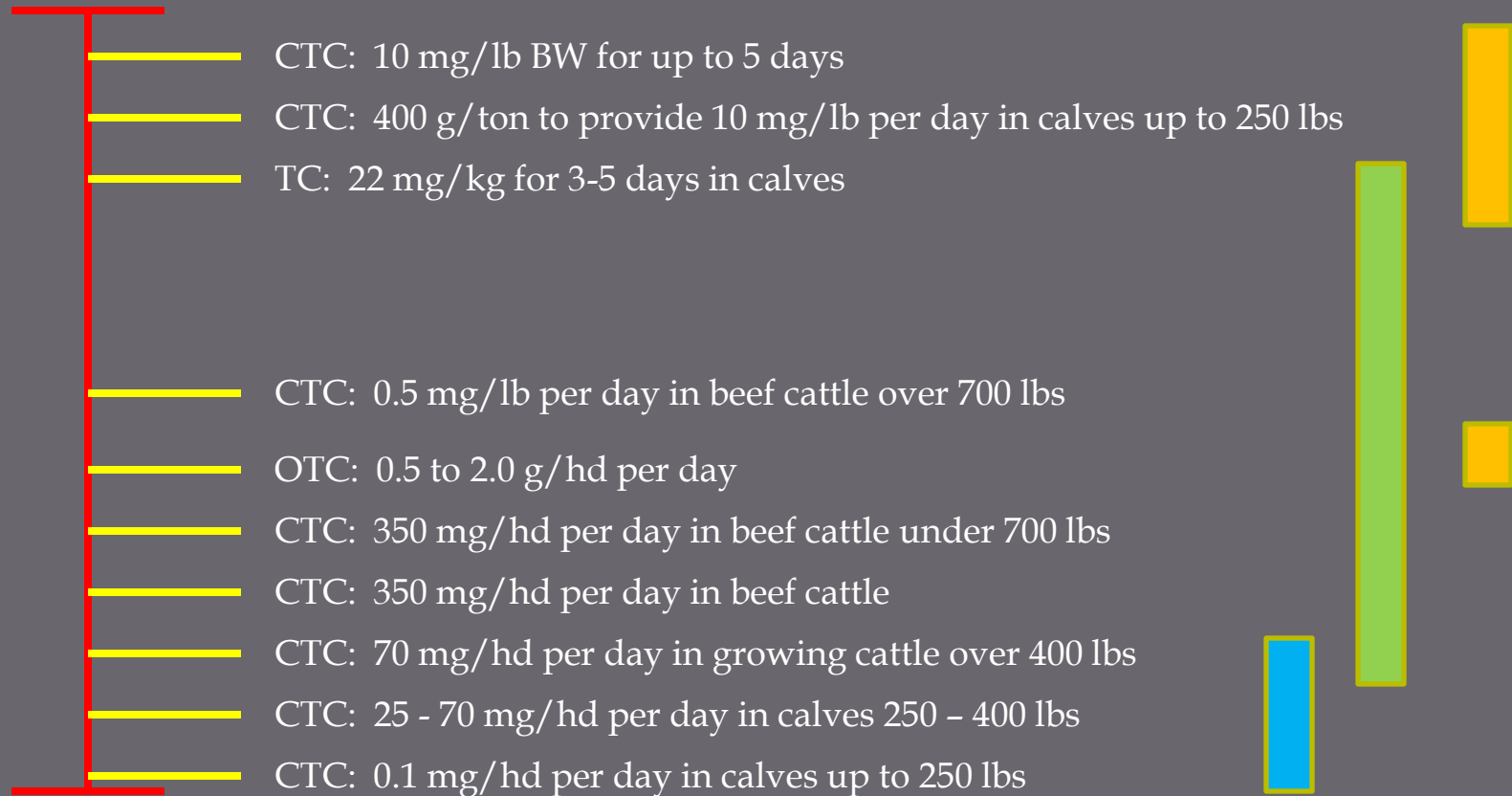
****Also labeled for swine respiratory disease**

Approved BRDC Antimicrobials

- ▣ For metaphylaxis (control)
 - Tilmicosin
 - Florfenicol
 - Ceftiofur crystalline free acid (CCFA)
 - Oxytetracycline 300 mg/ml
 - Tulathromycin (2005)
 - Gamithromycin (2011)
 - Tildipirosin (2012)
 - Enrofloxacin (2012)

U. S. CTC, TC and OTC Cattle Approval Examples

 Feed efficiency/Rate of gain  Prevention/Control  Treatment



These are not all of the CTC, TC, and OTC indications, but are selected to illustrate the regimen range.

Apley MD, et al. Use Estimates of In-Feed Antimicrobials in Swine Production in the United States. Foodborne Path Dis 3(9):2012.

TABLE 5. NATIONAL ESTIMATE OF TOTAL KILOGRAMS OF SWINE IN-FEED ANTIMICROBIALS FOR ALL PRODUCTION CYCLES IN A YEAR BY ANTIMICROBIAL AND REASON

	Antimicrobial	Growth promotion	Prevention	Therapy	Any reason 'yearly basis'
Antimicrobials not listed in FDA/CVM Guidance 152 Appendix A	Arsanilic acid	0	10,494	0	10,494
	Bacitracin	72,760	11,032	24,914	108,707
	Bacitracin zinc	4,844	0	0	4,844
	Bambermycins	543	0	0	543
	Carbadox	3,787	7,409	12,923	24,119
	Roxarsone	461	51	4,456	4,967
	Sulfamethazine ^a				
	as Chlortetracycline/Sulfamethazine/ Penicillin G (ASP)	2,735	3,663	1,148	7,546
	as Tylosin/Sulfamethazine	7,500	149	3,460	11,109
	Sulfathiazole ^a				
Antimicrobials or classes listed as Highly Important in Guidance 152 Appendix A	as Chlortetracycline/Sulfathiazole/ Penicillin G (CSP)	942	14,673	3,784	19,398
	Tiamulin	2,393	6,770	3,571	12,734
	Chlortetracycline ^b				
	as Chlortetracycline alone	83,331	206,076	217,622	507,029
	as Chlortetracycline/Sulfathiazole/ Penicillin G (CSP)	942	14,673	3,784	19,398
	as Chlortetracycline/Sulfamethazine/ Penicillin G (ASP)	2,735	3,663	1,148	7,546
	Lincomycin ^c	356	4,246	20,844	25,446
	Neomycin				
	as Neomycin/Oxytetracycline	4,068	2,632	16,394	23,094
	Oxytetracycline ^b				
	as Oxytetracycline alone	2,615	31,699	97,547	131,862
	as Neomycin/Oxytetracycline	4,068	2,632	16,394	23,094
	Penicillin				
	as Chlortetracycline/Sulfathiazole/ Penicillin G (CSP)	471	7,336	1,892	9,699
Antimicrobials or classes listed as Critically Important in Guidance 152	as Chlortetracycline/Sulfamethazine/ Penicillin G (ASP)	1,367	1,832	574	3,773
	Virginiamycin ^d	26,108	54,858	493	81,459
	Tilmicosin ^e	1,068	46,906	22,786	70,761
	Tylosin ^e				
	as Tylosin alone	25,641	37,893	91,160	154,694
	as Tylosin/Sulfamethazine	7,500	149	3,460	11,109

533,973

154,956

165,803

^aOnly potentiated sulfonamides are listed in Guidance 152, Appendix A.

^bThe tetracycline class representative in Guidance 152, Appendix A is tetracycline.

^cThe lincosamide class representative listed in Guidance 152, Appendix A is clindamycin.

^dThe streptogramin class representative in Guidance 152, Appendix A is dalfopristin/quinupristin.

^eThe macrolide class representatives listed in Guidance 152, Appendix A are erythromycin, azithromycin, and clarithromycin. Antimicrobials are grouped according to classification or lack of classification in Appendix A of FDA/CVM guidance 152.

Not listed in G152 Appendix A

<i>Antimicrobial</i>	<i>Growth promotion</i>	<i>Prevention</i>	<i>Therapy</i>	<i>Any reason 'yearly basis'</i>
Arsanilic acid	0	10,494	0	10,494
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Listed in G152 Appendix A

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^bThe tetracycline class representative in Guidance 152, Appendix A is tetracycline.

^cThe lincosamide class representative listed in Guidance 152, Appendix A is clindamycin.

^dThe streptogramin class representative in Guidance 152, Appendix A is dalfopristin/quinupristin.

^eThe macrolide class representatives listed in Guidance 152, Appendix A are erythromycin, azithromycin, and clarithromycin. Antimicrobials are grouped according to classification or lack of classification in Appendix A of FDA/CVM guidance 152.

Regulatory Happenings

- ▣ Cephalosporin ELDU prohibition
 - Any application OK but only label regimen
 - However, no prevention (control OK)
- ▣ Guidance 209
 - Growth promotants are gone
 - All antimicrobials under veterinary guidance
- ▣ Guidance 213
 - How they are going to do it
- ▣ Draft VFD guidance
 - We need to give input

Regulatory Happenings

- ▣ Input on gathering farm-level use data



